Lattice Monte Carlo Models of Cellular Assembly Systems

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The combination of an improved understanding of molecular systems, methods for mathematical modeling and simulation, and computing power is generating great promise for predictive models of increasingly complex cellular biological systems. Classically, such problems have been approached primarily with differential equation representations of the time progress of reaction systems that are parameterized by kinetic rate constants. Such models have been very successful in certain domains, but abstract away details that are likely to be critical in other environments. One key factor commonly missing from such models is an account of the effects of spatial constraints on molecular reactions. Cellular environments and their sub-cellular compartments are generally small, densely-packed, and irregularly structured spaces that are subject to large local concentration differences. These factors are likely to be lacking from both the classic systems biology models and in the *in vitro* experiments generally used to parameterize them. Spatial constraints are particularly likely to be an issue when studying self-assembly systems, which must construct comparatively large and regular structures within these small, irregular spaces. Understanding molecular interactions in a spatiotemporal environment is intertwined with multiple diseases, including cancer, heart disease, and neurodegenerative diseases. Furthermore, accurately modeling self-assembly behavior in cellular environments can be expected to be crucial to the broader goal of building reliable models of overall cellular dynamics, given the ubiquity of self-assembly systems in cell biology and their importance to many key cell processes.

The goals of our work are to develop modeling methods that can account for these challenging spatial constraints, characterize their performance relative to space-blind differential equation models, and determine the conditions under which spatial considerations are necessary to reliably capture self-assembly dynamics. To this end, we have developed a general technique for lattice Monte Carlo modeling of protein assemblies forming within spatially constrained environments. In this technique, proteins are presumed to occupy discrete points in a space and are allowed to move about the space and interact with one another according to probabilistic rules of behavior. Such a simplified model allows us to capture key aspects of self-assembly dynamics in a highly tractable computational system. We have initially applied this model to a system of two-dimensional linear polymer assembly that is meant to model the assembly of actin fibrils constrained to a two-dimensional surface. Comparisons of this model to a differential equation model of the same system lacking spatial constrains reveals convergence between the models under conditions of slow reaction rates, low concentrations, and large volumes, but noticeable divergence as we move to the high concentrations and small spaces one might find in cells and sub-cellular compartments. These results suggest the need for continuing to work on exploring the effects of spatial constraints on assembly reactions, improving methods to model these effects, and characterizing the conditions under which these methods will be necessary for reliable quantitative modeling of self-assembly dynamics in cellular environments.

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